Absorption and bioavailability of nebulized morphine

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ABSORPTION AND BIOAVAILABILITY OF NEBULIZED MORPHINE

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SUMMARY

During anaesthesia seven patients received a bolus of morphine 10 mg injected into the nebulization reservoir placed between the tracheal tube and the anaesthetic circle (IH). Five days after operation the same seven patients received morphine 10 mg i.m. On both occasions, venous blood samples were taken before and every 15 min after administration over 4.5 h for measurement of free morphine immunoreactivity by radioimmunoassay. There was marked individual variation in the serum morphine concentrations produced following each route of administration. The maximum serum morphine concentration following inhaled morphine was approx. six times lower than that after morphine i.m. and the time of occurrence differed significantly ($P < 0.001$). The individual relative bioavailabilities of inhaled morphine varied from 9% to 35%, with a mean of 17%.

Recently it has been shown that postoperative analgesia can be produced and maintained by the inhalation of nebulized morphine [1]. However, the use of this technique in a larger number of patients revealed that pain relief was not always satisfactory. The aim of this study therefore was to evaluate the bioavailability of morphine administered by inhalation.

METHODS AND RESULTS

Following institutional approval and informed written consent, seven patients were studied (two males, five females, mean age 49 (SD 19) yr, mean weight 64 (SD13) kg) during abdominal surgery with 66% nitrous oxide and enflurane in oxygen, plus neuromuscular blockade. All patients suffered from rheumatic diseases requiring chronic non-opioid analgesic treatment. During operation, morphine 10 mg in sodium saline 5 ml was injected into the reservoir of a standard nebulizer (B+P Gmbh, 5206 Neunkirchen-Seelscheid 2, FRG; particle size approx. 5 μm with an oxygen flow of 5 litre min^{-1}) which was placed between the tracheal tube and the semi-closed anaesthetic breathing system with soda-lime. Mean nebulization time was 42 (SEM 3.9) min. The lungs were ventilated to achieve normocapnia with a tidal volume of 10 ml/kg body weight and ventilatory rate of 12 b.p.m.

Pain in the early postoperative period was treated with non-morphine analgesia in order to allow almost complete elimination of the morphine given by nebulization (IH). Upon complaint of pain on the 5th day after operation, morphine 10 mg was administered i.m. into the gluteus maximus (IM). Venous blood samples were taken before and every 15 min for 4.5 h after the two morphine administrations for measurement of free morphine immunoreactivity by radioimmunoassay (Diagnostic Products Corporation, Los Angeles, cross reactivity to morphine-3-glucuronide 0.22%).

Pharmacokinetic data were calculated for each subject. Maximum serum concentration of morphine (C^{max}) and the time of its occurrence (T^{max}) were obtained from the serum concentration-time data. The individual elimination half-lives of the terminal phase of the concentration–time curves ($T_{\frac{1}{2}}^{\beta}$) were determined by linear regression analysis when the terminal data points (at least

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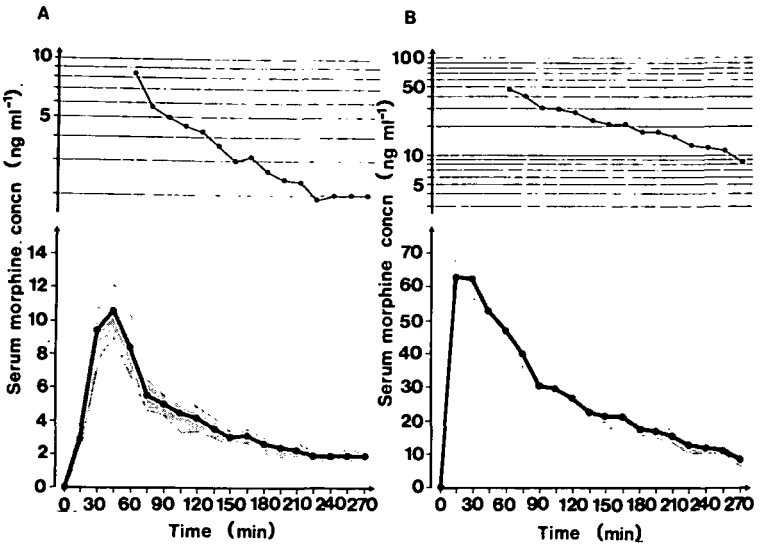

FIG. 1. Mean serum morphine concentrations (SEM) after administration of (A) nebulized morphine 10 mg by inhalation and (B) morphine 10 mg i.m. in the same seven patients.

TABLE I. *Pharmacokinetic details of seven patients who received nebulized morphine 10 mg by inhalation (IH) and i.m. morphine 10 mg (IM) on two separate occasions. %CV = Coefficient of variation*

Patient No.		C^{max} (ng ml^{-1})	T^{max} (min)	$T_{\frac{1}{2}}^{\beta}$ (min)	AUC (ng ml^{-1} min)	F(%)
1	IH	9.0	44.4	144	1009	9.5
	IM	70.2	28.7	143	10631	
2	IH	15.0	56.8	104	1544	15.1
	IM	86.5	21.7	134	10242	
3	IH	21.4	37.3	180	3031	34.6
	IM	56.9	54.6	80	8755	
4	IH	9.8	44.0	123	945	9.7
	IM	101.3	20.4	49	9787	
5	IH	12.1	55.8	142	1617	19.7
	IM	60.4	20.1	105	8198	
6	IH	7.2	39.1	86	899	8.9
	IM	60.9	25.2	150	10090	
7	IH	8.3	40.1	288	1320	18.8
	IM	58.3	25.2	79	7023	
Mean	IH	11.8	45.5	152.4	1480.7	16.6
	IM	70.6	28.0	105.7	9246.6	
%CV	IH	42.0	17.4	44.0	50.1	54.8
	IM	24.1	43.4	36.1	14.1	

three) plotted on a logarithmic axis declined linearly. The area under the curves (AUC) was calculated by the linear trapezoidal method and was extrapolated to infinity by integrating the terminal elimination phase. Individual relative bioavailabilities of the inhaled morphine (F) were calculated by dividing the area under the curve after morphine inhalation (IH) by that after i.m. (IM) administration for each subject.

For statistical analysis, the non-parametric Wilcoxon matched pairs signed rank test was used.

There was marked interindividual variation in the serum morphine concentrations when morphine was given by either inhalation or i.m. injection. In most of the patients receiving nebulized morphine the maximum serum concentration was reached within 45 min, when the

mean peak concentration was 10.7 (SEM 1.6) ng ml^{-1}; the maximum serum concentration independent of time was 11.8 (SEM 1.9) ng ml^{-1} (fig. 1A, table I). In contrast, following i.m. administration of morphine a mean serum morphine concentration of 63.5 (SEM 6.2) ng ml^{-1} was reached within 15 min; the maximum serum concentration independent of time was 70.6 (SEM 6.4) (fig. 1B, table I). The maximum serum morphine concentration (C^{max}) after inhalation was approximately six times lower than that after i.m. administration and the times of their occurrence differed significantly ($P < 0.001$).

The relative bioavailability of morphine following inhalation was approximately 9–35 %, with a mean of approximately 17 %.

COMMENT

Gaensler and colleagues [2] observed that only 7–30 % of a nebulized drug inhaled into the lungs was absorbed into the circulation, as at least 50 % of the drug is lost on expiration. In addition, loss of drug results from absorption onto equipment and some morphine may be taken up by endothelial cells [3]. Furthermore, patients may swallow drug present in the pharynx.

Our results of the bioavailability of inhaled nebulized morphine support previous observations in which a five-fold difference in serum morphine concentration was found following the inhalation and i.v. administration of morphine given to achieve similar levels of postoperative analgesia[1]. Plateau morphine concentrations of approximately 4 ng ml^{-1} and 20 ng ml^{-1} were achieved within 1 h after commencing inhalation or i.v. treatment, respectively [1]. It is tempting to speculate, therefore, that the mode of analgesia after inhalation of morphine differs from that achieved following other parenteral routes of administration.

The low serum morphine concentrations observed after inhalation of nebulized morphine were found to be associated with fewer side-effects than those seen after i.v. administration. Moreover, it has been found recently that the inhalation of morphine does not increase resting airway resistance [4], which was thought previously to be a severe side-effect of this method.

The great interindividual differences in systemic absorption and the fact that lower serum concentrations of morphine occur after inhalation than following oral [5] or rectal [6] administration suggest that consistent pain relief cannot be anticipated with nebulized morphine and that repeated administration may result in potential hazard.

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